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**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

PDL BIOPHARMA, INC. and EKR
THERAPEUTICS, INC.,

Plaintiffs,

-against-

SUN PHARMACEUTICAL INDUSTRIES
LTD.,

Defendant.

Civil Action No. 07-CV-1788

Hon. Katharine S. Hayden, U.S.D.J.
Hon. Patty Shwartz, U.S.M.J.

**REVISED
~~PROPOSED~~ JOINT FINAL
PRETRIAL ORDER**

This matter having come before the Court for a pretrial conference pursuant to Rule 16 of the Federal Rules of Civil Procedure, the following Pretrial Order is hereby entered:

1. JURISDICTION (Set forth specifically.)

This lawsuit is a civil action for patent infringement arising under the patent laws of the United States, including, but not limited to, 35 U.S.C. § 271 *et seq.*, and 21 U.S.C. § 355. This Court has subject matter jurisdiction over this case pursuant to the patent laws of the United States and 28 U.S.C. §§ 1331 and 1338(a).

2. **PENDING/CONTEMPLATED MOTIONS** (Set forth all pending or contemplated motions, whether dispositive or addressed to discovery or the calendar. Also set forth the nature of the motion. If the Court indicated that it would rule on any matter at pretrial, summarize that matter. Each party's contemplated in limine motions should also be set forth.)

A. Plaintiffs' Motions:

i. EKR's Cross-Motion for Summary Judgment of Infringement

On August 1, 2008, Plaintiffs PDL BioPharma, Inc. ("PDL") and EKR Therapeutics, Inc. ("EKR Therapeutics") (collectively, "EKR") filed their cross-motion for summary judgment of infringement. That motion has been fully briefed and is currently pending before the Court.

ii. EKR's Opposition to Sun's Motion for an Early Trial Date

On June 11, 2008, Defendant Sun Pharmaceutical Industries Ltd. ("Sun") submitted a letter to the Court requesting an early trial date. On July 3, 2008, EKR submitted a letter to the Court in opposition to that request. As explained in EKR's submission, Sun has received numerous deficiency letters from the United States Food and Drug Administration ("FDA") indicating that its generic product is not approvable in its current form. (*See* 7/3/2008 Letter from Charles M. Lizza to The Honorable Katharine S. Hayden). Because of the regulatory deficiencies related to Sun's product, as well as the pendency of the fully-briefed cross-motions for summary judgment regarding infringement, this Court should adjourn any trial of this matter at this time until such time as the Court renders a decision on the pending motions or Sun resolves its regulatory issues.

Since EKR filed its July 3, 2008 letter, the FDA has issued Sun two additional deficiency letters that reinforce the likelihood that Sun will not receive approval for its product as currently formulated. In an August 8, 2008 deficiency letter, the FDA explained that the current "test batch" of Sun's product – the critical batch upon which the FDA bases its technical review of the application – is "unacceptable," and as a result, Sun will (at a minimum) have to manufacture

and test an entirely new batch before it can possibly obtain approval. Moreover, the FDA stated that its review of Sun's ANDA is far from complete and that additional deficiencies will be forthcoming in other letters. Most importantly, the FDA has stated on at least two occasions that Sun's product will not be approved unless it contains the same amount of sorbitol in the same concentration as Cardene[®] I.V. If Sun modifies its product according to this FDA requirement, Sun's product will, without question, literally infringe the claims of the patent-in-suit – United States Patent No. 5,164,405 (“the ‘405 patent”). Because of the regulatory uncertainty surrounding even tentative approval of the Sun ANDA, the pendency of the fully briefed cross-motions for summary judgment regarding infringement, and the short remaining life of the ‘405 patent, this Court should adjourn any trial of this matter at least until such time as the Court renders a decision on the pending motions for summary judgment or Sun resolves its myriad approval issues.

iii. Motion *in Limine* to Preclude the Testimony of Sun's Proffered Expert on the Law, Mr. Godici

Sun designated Nicholas Godici as an expert on (1) “rules, practices, and procedures before the United States Patent and Trademark Office (“USPTO”), including the standards for patentability, and the application of those rules, practices, standards, and procedures to the evidence in this case” and (2) “the prosecution history of U.S. Patent No. 5,164,405.” (Godici Rep. at ¶ 1). By his own admission, however, Mr. Godici's opinions go far beyond the basics of Patent Office practice and procedure. In fact, an entire section of his report is devoted to an analysis of the Supreme Court's *KSR v. Teleflex* decision, even though Mr. Godici is not a lawyer and has had no formal legal training. (See Godici Tr. at 46:21). Another section of his report is dedicated to a “summary” of the prosecution history of the ‘405 patent, even though Mr. Godici candidly admitted at his deposition that he is not a person of ordinary skill in the art of

the '405 patent. For these reasons, EKR intends to file a motion precluding from testifying at trial.

First, it is the exclusive province of the Court to interpret the law and to determine what legal standards apply in this case. No "expert" opinions on the law are necessary or appropriate to instruct the Court. Indeed, this Court recently explained that the rule prohibiting experts from offering legal opinions is "so well established that it is often deemed a basic premise or assumption of evidence law – a kind of axiomatic principle." *Casper v. SMG*, 389 F. Supp. 2d. 618, 621 (D.N.J. 2005) (internal citations omitted). *See also Pfizer Inc. v. Teva Pharms.*, 2006 WL 3041097, at *2, *7 (D.N.J. Oct. 26, 2006) (precluding patent law expert from testifying about the law generally or offering legal conclusions that follow from facts). On this basis alone, Mr. Godici should not be allowed to testify.

Further, Mr. Godici should be precluded from offering any opinions concerning interpretation of the prosecution history of the '405 patent or what he believes are the relevant portions of the prosecution history. As a matter of law, the prosecution history must be interpreted from the perspective of one of ordinary skill in the art of the inventions claimed in the '405 patent. *See Paul Corp. v. Micron Separations*, 66 F.3d 1211, 1224 (Fed. Cir. 1995). At his deposition, Mr. Godici freely admitted that he is not a person of ordinary skill and that he has absolutely no experience in the relevant technology involved in this case. (Godici Tr. at 241:15-17 ("I don't believe I would be considered one of ordinary skill in the art.")). *See also id.* at 153:20-21) (no experience in chemistry); *id.* at 153:25-154:2 (no experience in pharmaceutical formulation); *id.* at 154:3-18 (no experience in medicine)). Federal Rule of Evidence 702 permits expert testimony only from a "qualified" expert who is knowledgeable about the relevant technology. Fed. R. Evid. 702; *Daubert v. Merrell Dow Pharms., Inc.*, 509 U.S. 137, 147 (1993)

(scientific testimony also must be relevant and reliable). As a result, Mr. Godici is unqualified to opine on any aspect of the prosecution history of the '405 patent.

iv. Motion in Limine to Preclude the Testimony of Sun's Proffered Economics Expert, Mr. Boghigian

In support of the commercial success of the inventions claimed in the '405 patent, EKR has offered the testimony of Dr. Joel Hay, a Professor of Pharmaceutical Economics and Policy at the University of Southern California and a Health Economics Consultant for the Rand Corporation. In an attempt to rebut Dr. Hay's opinions, Sun has designated Harry C. Boghigian, a business executive who has absolutely no expertise in economics, much less the highly specialized field of pharmaceutical economics. Moreover, according to his *curriculum vitae*, the vast majority of Mr. Boghigian's experience is limited to time spent in the sales and marketing divisions of a single pharmaceutical company. To provide testimony at trial, an expert must be qualified in the relevant technology. Fed. R. Evid. 702 (permitting testimony by a witness "qualified as an expert"). Mr. Boghigian does not come anywhere close to meeting this standard and should be precluded from testifying at trial.

v. Motion in Limine to Preclude Sun from Introducing any Evidence or Argument Regarding Prior Offer for Sale

Plaintiffs anticipate that Sun may attempt to introduce evidence or argument regarding an alleged prior offer for sale of the inventions claimed in the '405 patent. To prevail on this theory of invalidity, Sun must introduce clear and convincing evidence. To date, the only support that Sun has offered for this defense is the expert opinion of Dr. Patrick DeLuca. At his deposition, however, Dr. DeLuca unequivocally stated that he is not opining that there has been a prior offer for sale of the nicardipine formulations claimed by the '405 patent. (See DeLuca Tr. at 97:17-22 (Q: "So you're not saying that there's been a prior offer for sale of the composition in the '405 patent?" A: "No.")). Without the testimony of Dr. DeLuca, Sun cannot possibly meet its

burden and should be precluded from introducing any evidence or argument regarding a prior offer for sale of the patented invention pursuant to Rules 402 and 403 of the Federal Rules of Evidence.

vi. Motion *in Limine* to Preclude Sun from Introducing Any Evidence or Argument Regarding the Veracity of Certain Statements Made During Prosecution or the State of Mind of the '405 Applicants

EKR anticipates that Sun may attempt to introduce evidence or argument regarding certain statements made during the prosecution of the '405 patent or the intent of the '405 applicants. In his expert report, Sun's expert Dr. Rhodes states that he was asked to "consider the veracity and reliability of certain submissions and/or statements the applicants made to the USPTO in an effort to obtain the patent." (Rhodes Rep. at ¶ 114). Further, Dr. Rhodes insinuates that the '405 applicants intentionally made false statements to the Patent Office during the prosecution of the '405 patent. These statements are wholly unsupported and intended only to incite speculation concerning the state of mind of the '405 applicants. As a matter of law, intent is not relevant to the issues of infringement and validity. Accordingly, these issues are not relevant to any claim or defense in this case, and should therefore be precluded under Rules 402 and 403 of the Federal Rules of Evidence.

vii. Motion *in Limine* to Preclude Sun from Introducing Any Evidence or Argument Regarding Any Alleged Benefits of Generic Drugs and/or Harms from Pharmaceutical Patents to Society

EKR anticipates that Sun may attempt to introduce evidence or argument that generic drugs benefit society by promoting competition among drug manufacturers, reducing the cost of medication, and increasing availability. EKR also anticipates that Sun may attempt to introduce evidence or argument that brand pharmaceutical companies prevent society from receiving the benefits of low-cost generic alternatives by obtaining and enforcing their patents to exclude

competition. Such evidence and argument is not relevant to any claim or defense asserted by EKR or Sun, and should therefore be precluded under Rule 402 of the Federal Rules of Evidence. Furthermore, the marginal probative value, if any, regarding such emotionally-charged and potentially politically-divisive topics is substantially outweighed by the danger of unfair prejudice under Federal Rule of Evidence 403. This is particularly so in this case where Sun has not obtained tentative approval of its product from the FDA, and is therefore not precluded from marketing a generic product because of the pendency of this lawsuit.

viii. Motion *in Limine* to Preclude Sun from Introducing any Evidence or Argument Regarding the Sale of a Pre-Mixed Bag Version of Cardene® I.V.

On August 1, 2008, EKR received FDA approval to market a version of Cardene® I.V. supplied in a premixed bag. At trial, Sun may attempt to introduce evidence or argument alleging that the introduction of the Cardene® I.V. premixed bag is an attempt by EKR to “switch the market” before the introduction of Sun’s generic nicardipine product. Such evidence or argument is not relevant to any claim or defense asserted by EKR or Sun, and should be precluded under Rules 402 and 403 of the Federal Rules of Evidence.

B. Defendant’s Motions:

Pending Motions

- i. Sun’s motion for summary judgment of noninfringement.**

Contemplated Motions

- ii. *Daubert* motion to preclude Plaintiffs’ testifying expert Dr. Thomas Foster from providing opinions regarding infringement and validity of U.S. Patent No. 5,164,405.**

Dr. Foster’s area of expertise is the evaluation of drugs after administration to the patient. He is therefore not qualified to render an expert opinion regarding the formulation of parenteral dosage forms, which is the subject matter of the patent-in-suit.

iii. *Daubert* motion to preclude Plaintiffs' testifying expert Dr. Marc Dickstein from providing an opinion regarding infringement of U.S. Patent No. 5,164,405.

Dr. Dickstein is a medical doctor whose area of expertise is the administration of parenteral drugs in the surgical setting. He is not qualified to render an expert opinion regarding the formulation of parenteral dosage forms, which is the subject matter of the patent-in-suit.

iv. *Motion in limine* to exclude evidence of commercial success as a secondary consideration of nonobviousness.

The commercial embodiment of the patent-in-suit, CARDENE® I.V., was first launched in 1992. Plaintiffs intend to provide sales information from 2002-2007 as evidence that the invention described in asserted claims 1-4 would not have been obvious back in February 1989 – when the application that led to the issuance of the '405 patent was first filed. Moreover, Plaintiffs are unable to establish a nexus between the commercial sales and the purportedly novel aspects of the claimed invention.

v. *Motion in limine* to exclude reference to Food and Drug Administration deficiency letters regarding Sun's Abbreviated New Drug Application as proof of infringement or validity of the patent-in-suit.

The Food and Drug Administration's evaluation of Sun's proposed ANDA product for safety and efficacy is not relevant to the legal issues regarding infringement and/or validity of the patent-in-suit.

3. STIPULATION OF FACTS (Set forth in numbered paragraphs all uncontested facts, including all answers to interrogatories and admission to which the parties agree.)

I. THE PARTIES

1. Plaintiff PDL is a publicly held corporation organized and existing under the laws of the State of Delaware, having its headquarters at 34801 Campus Drive, Fremont, California 94555.

2. PDL is registered to do business in the State of New Jersey and has offices at 2035 Lincoln Highway, Suite 2150, Edison, New Jersey 08817.

3. PDL is engaged in the discovery, development, and commercialization of therapies for severe or life-threatening illnesses.

4. Plaintiff EKR is a privately held specialty pharmaceutical company organized and existing under the laws of the State of Delaware, having its headquarters at 7 East Frederick Place, Cedar Knolls, New Jersey 07927.

5. EKR is engaged in the acquisition, development and commercialization of proprietary prescription products for use in acute-care hospital settings.

6. Defendant Sun is a corporation organized and existing under the laws of India, having a principal place of business at Acme Plaza, Andheri-Kurla Road, Mumbai, India 400-059, India.

7. Sun Pharmaceutical Industries Inc. ("Sun Pharmaceuticals") is a wholly owned subsidiary of Sun and has a manufacturing facility at 270 Prospect Plains Road, Cranbury, NJ 08512.

8. Sun Pharmaceuticals owns a facility at 6 Hollywood Court, South Plainfield, New Jersey 07080 and maintains a registered agent, Corporation Service Company, at 830 Bear Tavern Road, West Trenton, New Jersey 08628.

II. BACKGROUND OF TECHNOLOGY

A. pH

9. pH is a measure of the acidity of a solution.
10. Acids are a class of compounds that tend to lower the pH of a solution.
11. Bases are a class of compounds that tend to raise the pH of a solution.
12. pH is typically reported on a scale of 1.0 to 14.0.
13. pH is commonly measured using a pH meter that is connected to an electrode that is suspended in the solution to be measured.

B. Calcium Channel Blockers

14. There are several classes of drugs that are used in the short-term treatment of hypertensive emergencies.
15. One class of drugs used in the short-term treatment of hypertensive emergencies is beta-blockers, such as labetalol and esmolol.
16. Another class of drugs used in the short-term treatment of hypertensive emergencies is nitrates, such as sodium nitroprusside and nitroglycerin.
17. In a comparative study between sodium nitroprusside and nicardipine hydrochloride for the control of hypertension in neurosurgical intensive care units, the Department of Neurosurgery at the University of Illinois at Chicago found that "[w]hen used for control of hypertension in patients with [subarachnoid] or [intracerebral hemorrhage], [nicardipine hydrochloride] and [sodium nitroprusside] were both safe and effective, but

patient[s] on [nicardipine hydrochloride] drip needed fewer dose adjustments and fewer additional medications.” (PDL0390577-80, Roitberg *et al.*, “Comparison of Intravenous Nicardipine and Nitroprusside for Control of Hypertension in the Neurological ICU: A Prospective Randomized Study of Safety, Efficacy and Cost,” Dept. of Neurosurgery, University of Illinois at Chicago (2007)).

18. Another class of drugs used in the short-term treatment of hypertensive emergencies is calcium channel antagonists (blockers), such as nicardipine hydrochloride, nifedipine, verapamil, and diltiazem.

19. Calcium crosses membranes through ion channels.

20. Calcium ion channel blockers are a class of drugs that decrease the amount of calcium crossing into the cells, and thereby reduce the strength of the heart contraction and relax the blood vessels, which in turn reduces blood pressure.

21. An electrical impulse is required to initiate the events leading to heart contraction.

22. This electrical activity is what is viewed on a standard electrocardiogram.

23. The entry of the positively-charged calcium ions into the heart cells changes the charge on the heart cell membrane.

24. Changes in this activity, by administration of calcium ion channel blockers, may result in changes in the electrical activity of the heart which may include slowing heart rate and the propagation of the electrical signal across the heart.

III. PATENT-IN-SUIT

25. The United States Patent and Trademark Office (“PTO”) issued United States Patent No. 5,164,405 (“the ‘405 patent”), entitled “Nicardipine Pharmaceutical Composition For Parenteral Administration,” on November 17, 1992.

26. The inventors of the '405 patent are Calum B. McFarlane, Alistair B. Selkirk, and Michael J. Dey.

27. Upon issuance, the '405 patent was assigned to Syntex (U.S.A.) Inc.

28. EKR is the assignee and owner of all rights, title, and interest in and to the '405 patent. PDL is a past owner of all rights, title, and interest in and to the '405 patent.

29. The '405 patent expires on November 17, 2009.

A. Specification

30. The '405 patent discloses pharmaceutical compositions suitable for parenteral administration containing nicardipine hydrochloride and processes for making those compositions.

31. The '405 specification discusses the problems associated with formulating a nicardipine solution for injection due to a reduction in solubility when a chloride containing compound is used as an excipient in the aqueous vehicle.

32. According to the '405 patent, the reduction in solubility may be attributed to a common ion effect between the nicardipine hydrochloride and the chloride ions of the vehicle, inhibiting ionization of the nicardipine hydrochloride and thereby reducing its solubility.

33. According to the '405 patent, this reduction in solubility often results in the formation of nicardipine free base that precipitates from solution and forms a yellow sticky substance.

34. The '405 patent teaches that the use of a non-chloride compound, such as sorbitol, avoids precipitation of nicardipine hydrochloride.

35. The '405 patent also teaches that the control of pH of the formulation is essential to maintain the aqueous solubility of nicardipine salts so that the desired therapeutic dose can be manufactured with suitable stability.

36. The '405 patent teaches that the effective pH range is between about 3.0-4.5.

37. The '405 patent explains that the pH can be controlled and maintained in the effective range by the use of a suitable buffer system, such as citric acid and sodium citrate.

38. The '405 patent explains that the buffer system is used to provide pH stability during manufacture and terminal sterilization, including autoclaving and long-term storage, and to ensure compatibility with a range of infusion fluids.

39. The '405 patent also discloses processes for producing pharmaceutical compositions suitable for parenteral administration containing nicardipine hydrochloride.

40. The '405 patent teaches that a physiologically and pharmaceutically acceptable buffer is first dissolved in an aqueous vehicle consisting essentially of water in an amount to maintain the pH at about 3.0 to 4.5.

41. The '405 patent teaches that at least 1mg/ml of nicardipine hydrochloride is then added to the buffered solution.

42. The '405 patent teaches that a physiologically and pharmaceutically acceptable non-chloride compound is also added to the buffered solution in an amount effective to render the pharmaceutical composition isotonic.

43. The '405 patent teaches that the pharmaceutical formulation is stable upon terminal sterilization by autoclaving.

44. The '405 patent also teaches that the pharmaceutical formulation is compatible with various infusion fluids, including 5% dextrose.

B. Claims

45. The '405 patent has nine claims.
46. Plaintiffs allege that Sun infringes claims 1-4.
47. Claims 1 and 3 are independent claims.
48. Claim 2 depends from claim 1.
49. Claim 4 depends from claim 3.
50. Claim 1 of the '405 patent recites:

In a process for producing a stable pharmaceutical composition containing nicardipine hydrochloride suitable for parenteral administration and useful in the treatment of disease conditions which may be alleviated by the administration of calcium channel blocking agents, which process comprises admixing a therapeutically effective amount of nicardipine hydrochloride and a pharmaceutically acceptable aqueous vehicle comprising at least a major proportion of water, the improvement comprising:

- (a) dissolving in an aqueous vehicle consisting essentially of water a physiologically and pharmaceutically acceptable buffer in an amount effective to maintain the pH of the pharmaceutical composition at about 3.0 to about 4.5, thereby forming a buffered solution; and
- (b) adding to said buffered solution at least 1 mg/ml of said therapeutically effective amount of nicardipine hydrochloride, and a physiologically and pharmaceutically acceptable non-chloride compound selected from saccharides, including sorbitol, mannitol, dextrose and glucose, and non-saccharides, including polyethylene glycol and glycerol, in an amount effective to render the pharmaceutical composition isotonic.

51. Claim 2 of the '405 patent recites:

The process of claim 1 further comprising the step of terminally sterilizing said pharmaceutical composition by autoclaving.

52. Claim 3 of the '405 patent recites:

A pharmaceutical composition suitable for parenteral administration to mammals and useful in the treatment of disease conditions which may be alleviated by the administration of calcium channel blocking agents, which composition comprises:

- (a) a physiologically and pharmaceutically acceptable non-chloride compound selected from saccharides, including sorbitol, mannitol, dextrose and glucose, and

non-saccharides, including polyethylene glycol and glycerol, in an amount effective to render the pharmaceutical composition isotonic;

(b) a physiologically and pharmaceutically acceptable buffer, selected from citrate, acetate, phosphate, and lactate buffers, in an amount effective to maintain the pH of the composition at about 3.0 to about 4.5;

(c) a pharmaceutically acceptable aqueous vehicle consisting essentially of water; and

(d) at least about 1 mg/ml nicardipine hydrochloride in solution herein.

53. Claim 4 of the '405 patent recites:

A composition according to claim 3 wherein the therapeutically effective amount of nicardipine hydrochloride is from about 0.5 mg/ml to about 10 mg/ml of aqueous vehicle and the aqueous vehicle is water (water for injection) alone.

C. Prosecution History

54. The '405 patent issued from United States Application No. 600,277 ("the '277 application"), filed October 22, 1990.

55. On August 18, 1989, the Examiner rejected the pending claims as obvious in light of four references: United States Patent No 3,985,758 ("the '758 patent"), United States Patent No. 4,711,902 ("the '902 patent"), European Patent Application No. 0162705 ("EP '705"), and German Offenlegungsschrift No. 3,316,510 ("German Offen.").

56. United States Patent No. 4,880,823 ("the '823 patent") is the counterpart to EP '705.

57. The Examiner described the '758 patent as "teach[ing] compositions and a method of preparing the same which differ from the composition herein merely in that the reference does not indicate the buffering of the solutions at a particular pH."

58. The Examiner described the '902 patent and EP '705 as "teach[ing] polyhydric compounds for rendering such compositions isotonic and that a pH of 2.5 to 5.5 is preferred."

59. The Examiner also described German Offen. as showing "the employment of buffers in closely related compositions."

60. The Examiner concluded that the pending claims were "obvious in the absence of evidence to the contrary to buffer the solutions at their optimum pH."

61. On December 12, 1989, Applicants responded to the Examiner's rejection.

62. Applicants explained that there is no disclosure or suggestion in the '758 patent of combining any buffer, particularly a buffer effective to maintain the pH at about 3.0-4.5, with the composition disclosed in the pending claims.

63. Applicants also argued that there was no disclosure or suggestion to use a buffer because there is no "recognition [in the '758 patent] of the problem involving precipitation of nicardipine hydrochloride from aqueous solution also containing a chloride compound."

64. Applicants distinguished the '902 patent as relating to "lipid emulsions of certain dihydropyridine medicinally active compounds," not "aqueous solutions containing nicardipine hydrochloride."

65. Applicants distinguished German Offen. as directed to parenteral formulations requiring "nimodipine, water, propyleneglycol and polyethyleneglycol, and ethanol useful for treatment of cerebral blood flow disorders."

66. Finally, Applicants distinguished EP '705 as not disclosing or teaching "the use of physiologically and pharmaceutically acceptable buffers useful to maintain the pH of the composition at 3.0-4.5."

67. In light of these distinctions, Applicants argued as follows:

Close examination of the secondary references [EP '705] and [German Offen.] cited and applied in the rejection which relate to aqueous solutions containing dihydropyridine compounds, compared with the later secondary reference [the '902 patent] and with references AL and AN cited by applicant to the Patent

Office, show that those skilled in the art with references [EP '705] and [German Offen.] in hand, did not combine the disclosure of references [EP '705] and [German Offen.] as the Examiner says is obvious but, rather, turned to lipid emulsion and liposome systems to obtain formulations for intravenous administration.

68. On March 5, 1990, the Examiner rejected the pending claims over the '758 patent, the '902 patent, EP '705, and German Offen., for "reasons of record."

69. The Examiner stated that "there is apparently no precipitation problem with either composition referred to by applicants. Moreover, the instant compositions do not call for a concentration of nicardipine hydrochloride which will present a solubility and/or stability problem."

70. On October 19, 1990, Applicants filed a Preliminary Amendment in response to the Examiner's March 5, 1990 rejection.

71. Applicants amended claim 1 to recite "at least about 1 mg/ml" nicardipine hydrochloride.

72. Applicants distinguished the formulation of the '758 patent as "unsatisfactory with regard to precipitation due to lack of pH control."

73. Applicants distinguished EP '705 as including "no disclosure of any buffer," and as "unstable with regard to pH because it lacks the buffer as presently claimed."

74. Applicants emphasized that "[t]hese solutions were subject to precipitation."

75. Finally, Applicants distinguished the '902 patent as relating to "lipid emulsions – not [aqueous] solutions – of dihydropyridines compounds and therefore solubility is not a concern at all in these prior art compositions."

76. Applicants explained that, by contrast, "Figure 2 of the present specification shows that buffer is essential to maintain pH of a nicardipine hydrochloride solution before and

after mixing with injection solution. Table 3, p. 17, also illustrates the inventors' findings that the pH of unbuffered solutions of nicardipine hydrochloride changes upon autoclaving."

77. On February 22, 1991, the Examiner again rejected the claims as obvious over the '758 patent, the '902 patent, EP '705, and German Offen.

78. On August 22, 1991, Applicants filed an Amendment in response to the Examiner's rejection.

79. Applicants explained that "the improved properties of the present composition with regard to stability during manufacture, storage, and mixture with other fluids are nowhere suggested by the prior art."

80. Additionally, Applicants submitted the Declaration of Alastair B. Selkirk describing the unexpected benefits or results of the claimed buffered composition, including "improved solubility of the nicardipine hydrochloride during preparation and terminal sterilization; long term stability of the preparations; and improved compatibility of the preparations with other fluids for injection."

81. Dr. Selkirk explained how he and his colleagues did not expect that the pH of the nicardipine solution would change during manufacturing and processing:

My co-inventors and I set out to make an injectable solution of nicardipine HCl having a concentration of at least about 1 mg/ml. We began with what we considered the obvious expedient of using isotonic saline. We then tried isotonic sorbitol. It was not until we discovered the pH changes which occur during the manufacturing process, both in formulation and in sterilization, that we appreciated the need for the present composition. At the outset of this project, the problems associated with pH changes during manufacturing, in particular, the pH changes which occur in different types of glass containers containing the present injectable solution, was not known in the literature or in practice.

82. Dr. Selkirk also explained how he and his colleagues were at first unsuccessful in solving the pH problem:

We first attempted unsuccessfully, to solve these problems by using different glass containers. We also had to solve the problem of the order of the addition of the ingredients of the composition, as it was discovered that the buffered solution must first be formed at the desired pH before the nicardipine HCl and isotonicity compound are added. In sum, even after the discovery that the pH needed to be maintained at a defined range, the successful use of the present buffer required more than routine experimentation to achieve.

83. Based on the Selkirk Declaration, the '405 Applicants discussed the unexpected benefits achieved by the invention of the '405 patent:

In addition, the enclosed Declaration of Alastair Selkirk provides a showing that the presently claimed buffered composition provides unexpected benefits over a non-buffered composition containing either sodium chloride or a polyhydric compound added to maintain isotonicity. These benefits are improved solubility of the nicardipine hydrochloride during preparation and terminal sterilization; long term stability of the preparations; and improved compatibility of the preparations with other fluids for injection. These benefits are as described in the specification. The circumstances of the discovery of the problems associated with pH changes and the solution of these problems are also set out as further evidence of the unobviousness of the present compositions.

84. Applicants concluded that "[t]he combination of Murakami et al., Serno AB, EPA-AM, and German Offen.-AO does not disclose or suggest a composition comprising a buffer selected from citrate, acetate, phosphate and lactate buffers for maintaining at least about 1 mg/ml nicardipine hydrochloride in solution in an aqueous vehicle at a pH between 3.0 and 4.5."

85. On September 23, 1991, the Examiner issued a final office action rejecting the claims over the '758 patent, the '902 patent, EP '705, and German Offen., for "reasons of record."

86. On April 28, 1992, in response to a telephone interview with the Examiner, Applicants amended the claims in accordance with the Examiner's requirements for allowance.

87. Applicants amended claims 1 and 3 to define the term "non-chloride" compound by reciting the compounds set forth in the specification.

88. As reported in the Interview Summary, "[i]t was agreed that the Final rejection under 35 USC 103 would be withdrawn for lack of motivation to make the combination, particularly in view of the Declaration regarding the existence of the precipitation problem."

89. On May 13, 1992, the Examiner allowed the pending claims.

D. Claim Construction

1. Isotonic

90. Red blood cells have a cellular membrane that separates the contents inside the cell from the liquid (*i.e.*, plasma) outside the cell.

91. When placed in a solution that has a lower concentration of solutes than the concentration of solutes inside the cell, red blood cells will swell (and possibly burst) as water moves across the cell membrane and into the cells.

92. By contrast, red blood cells that are placed in a solution that has a higher concentration of solutes than inside the cell will shrink as water moves across the cell membrane and out of the cell.

93. Finally, red blood cells that are placed in a solution that has a comparable concentration of solutes as the solution inside the cell will retain their shape with little or no net movement of water across the cell membrane.

94. The term osmolality is a reflection of the amount of the solutes in a particular solution.

95. Osmolality can be assessed both *in vivo* and *in vitro*.

96. Osmolality is a quantitative property (often measured in units of milliOsmoles per kilogram solvent) that, by itself, does not involve a comparison between two different solutions.

97. The '405 specification explains that the term "isotonic" is used "in its conventional sense" to mean "a fluid corresponding to body fluids including blood and lacrimal fluid" and cites Remington's Pharmaceutical Sciences. ('405 patent at 3:56-62).

98. The '405 specification also refers to a commonly used parenteral infusion fluid in its discussion of isotonic.

99. The '405 specification describes "isotonic" as "normally having an osmotic pressure which is often described as corresponding to that of a 0.9% solution of sodium chloride." ('405 patent at 3:62-64).

100. For example, the '405 specification describes the therapeutic advantages of parenteral dosage forms (*id.* at 1:30-44) and the risks to patients of formulations with "physical, chemical and therapeutic incompatibilities" (*Id.* at 2:8-24).

101. *Remington's Pharmaceutical Sciences*, 17th Edition, 1985 confirms that "[o]bservation of the behavior of human erythrocytes when suspended in a solution is the ultimate and direct procedure for determining whether the solution is isotonic, hypotonic, or hypertonic."

102. *Remington's Pharmaceutical Sciences*, 17th Edition, 1985 concludes that "isotonicity infers a sense of physiologic compatibility where isoosmoticity need not."

103. *Dorland's Medical Dictionary*, 27th Edition, 1988 defines "isotonic" as "a biological term denoting a solution in which body cells can be bathed without a net flow of water across the semipermeable cell membrane. Also, denoting a solution having the same tonicity as some other solution with which it is compared, such as physiologic salt solution and the blood serum."

104. Lachman, et al., *The Theory and Practice of Industrial Pharmacy*, 3rd Edition, 1986 defines isotonicity in terms of biological systems:

Although the freezing point depression of the solution is most frequently used to determine whether a solution isotonic, isotonicity actually depends on the permeability of a living semipermeable membrane that separates the solution from a biologic cell system. Most frequently, for sterile pharmaceutical preparations, the membrane concerned is the one enclosing the red blood cells. Therefore a preparation cannot be considered to be isotonic until it has been tested in a biologic system.

105. Sun's measurements of the osmolality of its nicardipine product in 5% dextrose dilutions range from between 252-270. (KRA 004736; '746 Application at Table 2).

2. Parenteral Administration

106. The '405 patent particularly points to the intravenous route of administration when describing the claimed composition as suitable for parenteral administration: "This invention relates to an aqueous pharmaceutical composition containing nicardipine hydrochloride in a therapeutically effective amount suitable for parenteral administration, especially intravenous administration." ('405 patent at 1:12-15).

107. In the General Background section of the specification, the '405 patent describes the advantages of injection over orally administered dosage forms: "Administration of a drug by injecting a pharmaceutical composition containing such drug – parenteral administration – affords a number of advantages" (*Id.* at 1:30-32).

108. One advantage of administration by injection is that an almost immediate response may be obtained by administering by intravenous injection a solution, usually aqueous, of the drug.

109. Another advantage of administration by injection is that the therapeutic response by a patient to a drug may be more readily controlled by administering the drug parenterally.

110. Another advantage of administration by injection is that a drug can be administered parenterally to a patient when it cannot be administered orally because of the unconscious or uncooperative state of the patient, or because of inactivation or lack of absorption in the intestinal tract.

111. Parenteral administration is defined by Stedman's Medical Dictionary, 24th Edition, 1982 as administration "[b]y some other means than through the gastrointestinal tract or lungs; referring particularly to the introduction of substances into an organism; i.e., by intravenous, subcutaneous, intramuscular, or intramedullary injection."

112. Parenteral administration is defined by Dorland's Medical Dictionary, 27th Edition, 1988 as administration that is "not through the alimentary canal but rather by injection through some other route, as subcutaneous, intramuscular, intraorbital, intracapsular, intraspinal, intrasernal, intravenous, etc."

IV. CARDENE® I.V.

113. EKR is the owner of all rights, title, and interest in and to New Drug Application ("NDA") 19-734.

114. Cardene® I.V. is the subject of approved NDA No. 19-734.

115. The United States Food and Drug Administration ("FDA") approved NDA No. 19-734 on or about January 30, 1992.

116. Pursuant to 21 U.S.C. § 355(c)(2), the '405 patent is listed in the FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* ("the Orange Book") in connection with Cardene® I.V.

117. Cardene® I.V. is a calcium ion influx inhibitor.

118. The active ingredient in Cardene® I.V. is nicardipine hydrochloride.

119. Cardene® I.V. is approved for the short-term treatment of hypertension when oral therapy is not feasible or desirable.

120. Cardene® I.V. was the first FDA approved intravenous calcium channel blocker for the treatment of hypertension.

121. Cardene® I.V. is a commercial embodiment of the '405 patent.

V. SUN'S NICARDIPINE PRODUCT

122. In June 2006, pursuant to 21 USC § 355(j), Sun filed Abbreviated New Drug Application No. 78-405 ("Sun's ANDA") with the FDA seeking approval to engage in the commercial manufacture and sale of injectable nicardipine hydrochloride ("Sun's nicardipine product").

123. Sun's ANDA includes a certification pursuant to 21 U.S.C. §355(j)(2)(A)(vii)(IV) stating that each claim of the '405 patent will not be infringed by the commercial manufacture, use or sale of Sun's nicardipine product.

124. Sun's nicardipine product is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable.

125. Sun's nicardipine product is a parenteral solution intended for intravenous injection.

A. Composition

126. The composition of Sun's nicardipine product is described in Sun's ANDA. (Sun's ANDA, § IV, SPIL 00022, § VII, SPIL 000116, 000118, 000120).

127. The functions of the active and inactive ingredients in Sun's nicardipine product are described in Sun's ANDA. (Sun's ANDA, § VII, SPIL 000116, 000118, 000120).

128. At the time of development of Sun's nicardipine product, Sun's formulators understood the function of the inactive ingredients. (SPIL 013759-60; 6/2/08 Bhowmick Dep. at 251:4-25; 6/3/08 Khopade Dep. at 105:10-106:10, 150:20-151:11, 196:4-199:15, 206:8-207:9.).

B. Manufacturing Process

129. The process for producing Sun's nicardipine product is described in Sun's ANDA.(Sun's ANDA, § XI, SPIL 000335).

C. Research and Development

130. Sun's ANDA identifies Cardene® I.V. as the reference listed drug.

131. The dosage form of Sun's nicardipine product is the same as Cardene® I.V.

132. During development of its nicardipine product, Sun reviewed information concerning the composition and properties of Cardene® I.V., including the '405 patent, the Summary Basis of Approval of NDA No. 19-734, and the package insert for Cardene® I.V.

133. Sun tested the physical and chemical properties of Cardene® I.V.

134. Sun conducted stability studies of Cardene® I.V. and examined the amount of nicardipine hydrochloride degradation over time.

135. Sun attempted to reproduce the stability characteristics of Cardene® I.V. in its nicardipine product.

136. Sun submitted the results of stability studies for a batch of its nicardipine product under accelerated storage conditions, long term storage conditions, and photostability conditions. (Sun's ANDA, § XVI, SPIL 001012-13, 001015, and 001017).

137. Sun also submitted the results of stability studies after dilution of its nicardipine product in compatible intravenous fluids. (Sun's ANDA, § XVI, SPIL 001019-23; KRA 004730-40).

138. Sun relied on the results of these studies to represent to the FDA that the stability of its nicardipine product after dilution is comparable to Cardene® I.V. for up to 24 hours. (Sun's ANDA, § XVI, SPIL 001019-23; KRA 004735-40; Bhowmick Dep. at 98:13-20; 138:18-141:23).

139. Sun also submitted admixture studies that compared the stability of nicardipine hydrochloride, the pH, and the tonicity of its nicardipine product as compared to Cardene® I.V. after dilution in compatible intravenous fluids. (SPIL 001018-23; KRA 004734-40).

140. Based on the results of the admixture studies, Sun represented to the FDA that its nicardipine product is "comparable" to Cardene® I.V. (Bhowmick Tr. at 189:20-192:12, 232:22-234:8).

141. Sun represented to the FDA that the tonicity of its nicardipine product is comparable to that of Cardene® I.V. after dilution in a compatible intravenous fluid. (Sun's ANDA § XVI, SPIL 001019-23; KRA 004735-40; Bhowmick Tr. at 98:13-20; 138:18-141:23).

142. Sun also performed a biostudy in healthy human volunteers comparing its nicardipine product to Cardene® I.V. (SPIL028439-28453).

143. The subjects of the biostudy received infusions of Sun's nicardipine product and Cardene® I.V. after dilution in 0.9% sodium chloride. (SPIL013002).

144. Based on the results of this biostudy, Sun represented to the FDA that its nicardipine product is bioequivalent to Cardene® I.V. (SPIL 028453; Bhowmick Tr. 57:18-58:2, 98:5-12, 265:21-270:23).

145. For purposes of demonstrating bioequivalence, Sun relied exclusively on data collected after dilution of its nicardipine product and Cardene® I.V. in compatible infusion fluids.

D. Use

146. Sun's nicardipine product includes a product label that must accompany each ampule that is shipped into commerce. (SPIL 00074, 000088-89).

147. The product label provides information about the drug product's pharmacology, indications for use, safety, efficacy, and dosage. (SPIL 000037-71, 000088-89).

148. Sun's nicardipine product is indicated to treat the same conditions as Cardene® I.V.

149. Sun's proposed product label is included in its ANDA. (SPIL 000065-66, 000089).

150. Sun made certain statements about the isotonicity of its nicardipine product in its pending motion for summary judgment. (Sun's 7/1/08 Mem. in Supp. Mot. Summ. J. at 2, 15).

151. Sun expects and intends that healthcare providers will use its nicardipine product in accordance with Sun's product label.

152. The only use for which Sun can market its nicardipine product is the use set forth in Sun's product label.

VI. SUN'S PATENT APPLICATION

153. On November 14, 2006, Sun filed United States Patent Application No. 11/598,746 ("the '746 application"), entitled "Nicardipine Injection Composition."

154. On May 17, 2007, the '746 application was published as United States Patent Application Publication No. 2007/0112041.

155. Sun's application is generally directed to "[a] nicardipine hydrochloride injection composition comprising sorbitol in amounts sufficient to stabilize the injection preparation and a

physiologically and pharmaceutically acceptable buffer, in an amount effective to maintain the pH of the composition at about 3.0 to about 4.5.” (‘746 application at Abstract).

156. Sun has identified the ‘746 application as covering the nicardipine product described in Sun’s ANDA. (5/30/08 Shrivastava Dep. at 214:2-215:1; 6/2/08 Bhowmick Dep. at 194:22-25, 196:5-16, 218:10-219:25).

157. The Background of the Invention section of the ‘746 application describes nicardipine hydrochloride as “a calcium ion influx inhibitor (slow channel blocker or calcium channel blocker) and is indicated for the short-term treatment of hypertension when oral therapy is not feasible or not desirable.” (‘746 application at 0002).

158. The ‘746 application identifies nicardipine hydrochloride as “available in the US as CARDENE I.V. for intravenous administration.” (*Id.* at 0003).

159. The ‘746 application also states that “CARDENE I.V. (ESP Pharma) for intravenous administration contains 2.5 mg/mL of nicardipine hydrochloride and is available as a sterile, non-pyrogenic, clear yellow solution in 10 ml ampoules for intravenous infusion after dilution.” (*Id.*).

160. The ‘746 application describes the ‘823 patent as relating to an injectable composition of nicardipine hydrochloride “comprising an aqueous nicardipine hydrochloride solution containing 0.04 to 0.6 W/V % nicardipine hydrochloride and 2 to 7 W/V % of a polyhydric alcohol and wherein the pH of said solution is from 2.5 to 5.” (*Id.* at 0004).

161. The ‘746 application further describes the ‘823 patent as follows:

The patent teaches that the problem of stability of nicardipine hydrochloride formulations associated with chloride containing isotonicising agents was resolved by dissolving nicardipine chloride in water together with 2 to 7 W/V % of a polyhydric alcohol and adjusting the pH of the solution to 2.5 to 5. The pH of the solution was controlled by a mineral acid such as hydrochloric acid and/or by a base such as sodium hydroxide. (*Id.*).

162. The '746 application notes that "it was found that upon autoclaving, the pH of the solution would change, leading to precipitation of the nicardipine." (*Id.*)

163. The '746 patent explains that the '405 patent "overcomes the problems associated with the compositions of [the '823 patent] in that the buffered composition of the '405 patent was stable upon terminal sterilization such as autoclaving." (*Id.* at 0005).

164. The '746 application states that "the prior art has achieved stable injection formulations of nicardipine hydrochloride using sorbitol as the isotonicity adjuster." (*Id.* at 0006).

165. The '746 application describes Sun's nicardipine product as providing an aqueous nicardipine hydrochloride injection composition "comprising sorbitol in lower amounts without compromising on stability and safety of the composition." (*Id.* at 0008).

166. The '746 application explains that "[t]he composition of the present invention uses sorbitol in amounts sufficient to act as a cosolvent for the nicardipine hydrochloride so as to prevent its precipitation and maintain stability of the composition. But the amount of sorbitol used is not sufficient to make the composition isotonic." (*Id.* at 0021).

167. The '746 application explains that "upon dilution with 0.9% sodium chloride or 5% dextrose, the composition becomes isotonic, so that the final composition which is administered to the patient does not cause irritation." (*Id.*).

168. The '746 application provides that the nicardipine hydrochloride is used in a "therapeutically effective amount," which is an amount "which when administered to mammals, especially human patients, will have a calcium entry blocking effect that will be useful to treat their disease conditions, that is, conditions which may be alleviated by the administration of

calcium channel blocking agents, especially cardiovascular and cerebrovascular disease conditions.” (*Id.* at 0022).

169. The composition of the ‘746 application uses “a polyhydric compound as a cosolvent for preventing precipitation of the nicardipine hydrochloride” in an amount that “is sufficient to prevent the precipitation of the nicardipine hydrochloride but is insufficient to make the composition isotonic.” (*Id.* at 0023).

170. The ‘746 application states that the pharmaceutically acceptable buffer “is useful over the desired dose range of the composition to provide ease of manufacture of the composition, to maintain pH stability during and after manufacture including terminal sterilization by autoclaves and thus to render the composition compatible with a range of infusion fluids.” (*Id.* at 0024).

171. The ‘746 application states that the pharmaceutical composition “may be available as a concentrate composition to be mixed with infusion fluids such as 0.9% sodium chloride or 5% dextrose before administration to the patient, or ready to use compositions which are premixed with infusion fluids such as 0.9% sodium chloride or 5% dextrose.” (*Id.* at 0026).

172. Example 1 of the ‘746 application describes how to make the disclosed composition. (*Id.* at 0028-0029).

173. The ‘746 application states that sorbitol is next added to the solution and stirred until dissolved. (*Id.*).

174. The ‘746 application states that sodium hydroxide is then dissolved in the solution. (*Id.*).

175. The ‘746 application states that the last step is to make up the volume of the composition with the WFI and the pH adjusted to 3.5 to 4.0, if required. (*Id.*).

176. Example 2 of the '746 application describes a "tonicity study" that was "carried out on the injection composition of example 1 and compared with the tonicity of the marketed injection composition CARDENE I.V." (*Id.* at 0030).

177. The '746 application reports "[t]he tonicity of the injection composition, concentrate and solutions obtained on dilution of 1 part of the concentrate injection composition in 24 parts of 0.9% sodium chloride or dextrose 5%." (*Id.*).

178. The '746 application states that "[i]t is evident that although the concentrate obtained in the present invention has lower tonicity as compared to CARDENE I.V., the diluted preparations (which are administered to patients) have comparable tonicity values." (*Id.* at 0031).

179. During prosecution of the '746 application, the Examiner issued an obviousness rejection in light of the '405 patent.

180. The '746 application states that "[i]t is a well-known fact that parenteral compositions should contain bare minimum excipients to avoid any possible side effects associated with the excipients and associated impurities in the excipient, since the compositions are introduced directly into the systematic circulation." ('746 Application at 0007).

VII. PROCEDURAL HISTORY

181. On or about March 2, 2007, Sun sent PDL a Notice of Certification ("Notice Letter") pursuant to section 505(j)(2)(B)(ii) of the Federal Food, Drug, and Cosmetic Act stating that Sun's ANDA product does not infringe the '405 patent literally or under the doctrine of equivalents.

182. Sun's Notice Letter states that "SUN alleges, and has certified to the FDA, that in its opinion and to the best of its knowledge, each claim of the '405 patent will not be infringed by the commercial manufacture, use or sale of the drug product described by Sun's ANDA."

183. On or about April 16, 2007, PDL filed a Complaint for Patent Infringement against Sun alleging infringement of the '405 patent.

184. On or about May 10, 2007, PDL filed a First Amended Complaint for Patent Infringement.

185. On or about July 13, 2007, Sun filed an Answer, Affirmative Defenses, and Jury Demand ("Sun's Answer").

186. Sun's Answer asserted affirmative defenses of noninfringement and invalidity of the '405 patent.

187. On or about May 19, 2008, EKR and PDL filed a Second Amended Complaint for Patent Infringement.

188. On or about May 28, 2008, Sun filed an Answer to the Second Amended Complaint, Affirmative Defenses and Counterclaim ("Sun's Amended Answer").

189. Sun's Amended Answer asserts affirmative defenses and counterclaims of noninfringement and invalidity of the '405 patent. Sun also seeks an award of attorneys fees under 35 U.S.C. § 285.

190. Plaintiffs filed a reply to Sun's Amended Answer on June 17, 2008.

191. Plaintiffs allege that Sun's manufacture, use, sale, or offer for sale of its nicardipine product infringes claims 1-4 of the '405 patent, either literally or under the doctrine of equivalents. Plaintiffs also seek attorneys' fees under 35 U.S.C. § 285. Plaintiffs are not asserting claims 5-9 in this action.

192. Sun denies that its nicardipine product infringes any claim of the '405 patent. Sun's counterclaim seeks a declaration that Claims 1-4 of the '405 patent will not be infringed by the manufacture, use or sale of Sun's nicardipine product.

193. Sun does not allege that the '405 patent is unenforceable.

VIII. INFRINGEMENT

A. Claim 1

194. Sun's nicardipine product is "useful in the treatment of disease conditions which may be alleviated by the administration of calcium channel blocking agents."

195. The process for making Sun's nicardipine product comprises "admixing a therapeutically effective amount of nicardipine hydrochloride and a pharmaceutically acceptable aqueous vehicle comprising at least a major proportion of water."

196. The process for making Sun's nicardipine product comprises "dissolving in an aqueous vehicle consisting essentially of water a physiologically and pharmaceutically acceptable buffer in an amount effective to maintain the pH of the pharmaceutical composition at about 3.0 to about 4.5, thereby forming a buffered solution."

197. The process for making Sun's nicardipine product comprises "adding to said buffered solution at least 1 mg/ml of said therapeutically effective amount of nicardipine hydrochloride."

B. Claim 2

198. Claim 2 includes all of the limitations of claim 1 and also requires "the step of terminally sterilizing said pharmaceutical composition by autoclaving."

199. The function of Sun's filtration method is to sterilize Sun's nicardipine product.

200. The result of Sun's filtration method is that Sun's nicardipine product is sterile.

C. Claim 3

201. Sun's nicardipine product is "useful in the treatment of disease conditions which may be alleviated by the administration of calcium channel blocking agents."

202. Sun's nicardipine product includes "a physiologically and pharmaceutically acceptable buffer, selected from citrate, acetate, phosphate, and lactate buffers, in an amount effective to maintain the pH of the composition at about 3.0 to about 4.5."

203. Sun's nicardipine product includes "a pharmaceutically acceptable aqueous vehicle consisting essentially of water."

204. Sun's nicardipine product includes "at least about 1 mg/ml nicardipine hydrochloride in solution."

205. The result provided by the non-chloride compound in claim 3 is that the pharmaceutical composition is isotonic.

D. Claim 4

206. Claim 4 includes all of the limitations of claim 3 and also requires that "the therapeutically effective amount of nicardipine hydrochloride is from about 0.5 mg/ml to about 10 mg/ml of aqueous vehicle and the aqueous vehicle is water (water for injection) alone."

IX. VALIDITY

A. EP '705

207. EP '705 is entitled "Injection of Nicardipine Hydrochloride and Production Thereof."

208. EP '705 was filed in the European Patent Office on May 21, 1985.

209. EP '705 published on November 27, 1985.

210. EP '705 is generally directed to "an injection of nicardipine hydrochloride having cerebral vascular dilator activity, coronary dilator activity, and anti-hypertension activity." ('705 application at 1).

211. EP '705 explains that although oral formulations of nicardipine hydrochloride existed before EP '705, "no satisfactory injection containing nicardipine hydrochloride [had] been developed. . . because the compound has reduced solubility in known isotonic aqueous injection media." (*Id.* at 1).

212. Specifically, EP '705 explains that "in the presence of sodium chloride, which is usually used as an isotonicizing agent for injections, it is only possible to obtain an aqueous nicardipine hydrochloride solution which is of too low concentration and/or of insufficient stability for satisfactory use as an injection." (*Id.*).

213. According to EP '705, the nicardipine formulation disclosed in EP '705 solves the solubility problem of the prior formulations.

214. EP '705 explains that they "found that when nicardipine hydrochloride is dissolved in water together with 2 to 7 w/v% of polyhydric alcohol, a stable isotonic aqueous solution of the nicardipine hydrochloride is unexpectedly obtained." (*Id.*).

215. Further, EP '705 provides that the nicardipine solution of EP '705 "preferably [has] a pH of 2.5 to 5.5." (*Id.*).

216. Specifically, EP '705 explains that "[e]ven when the pH of the solution as initially formed is from 2.5 to 5.0 or 5.5, it may be preferred to adjust the pH to a specific desired value, e.g. 3.0, 3.5 or 5.0." (*Id.* at 2).

217. In addition, EP '705 states that "[t]he injection of this invention can be prepared by dissolving predetermined amounts of nicardipine hydrochloride and polyhydric alcohol in

water, e.g. at 50°C to 60°C, adjusting the pH (if necessary or desired), preferably to about 3.5, and then adjusting the volume of the solution to a predetermined volume by the addition of water.” (*Id.* at 2-3).

218. EP ‘705 further explains that “[t]he pH of the solution can be controlled by mineral acid such as hydrochloric acid or, as the case may be, by base such as sodium hydroxide or sodium hydrogencarbonate.” (*Id.* at 3).

219. Finally, EP ‘705 explains that the nicardipine solution made according to the disclosed process “can be stably stored for a long time without change in quality.” (*Id.*).

220. Further, EP ‘705 reports stability data at 100°C for up to 10 hours at pH 3.0, 4.0, and 5.0. (*Id.* at 7).

B. EP ‘475

221. EP 0149475 (“EP ‘475”) is entitled “Medicaments for the Treatment and Prevention of Liver Damage.”

222. EP ‘475 was filed in the European Patent Office on January 11, 1985 and was published on July 24, 1985.

223. EP ‘475 is generally directed to the use of nicardipine “for the treatment and prevention of liver damage induced by drugs, toxic chemicals, poisons, radiation, alcohol and viruses.” (‘475 application at Abstract).

224. EP ‘475 discloses that “nicardipine and nicardipine salts, particularly nicardipine hydrochloride, are active in diminishing the symptoms appearing during the liver damage and injury.” (*Id.* at 5).

225. EP ‘475 also discloses that “medicaments containing these compounds significantly decrease the elevated level of liver enzymes, such as, for example glutamic-

oxalacetic transaminase (GOT), glutamic-pyruvic transaminase (GPT) and sorbitol dehydrogenase (SDH). These medicaments also lower the bilirubin level and decrease the magnitude of hepatocellular necrosis.” (*Id.*).

226. EP ‘475 also discloses that “nicardipine and nicardipine salts, particularly nicardipine hydrochloride, administered before the liver damage occurred, effectively prevent the increase in liver enzymes and bilirubin and is thus useful in obviating the liver damage.” (*Id.* at 4).

227. Moreover, EP ‘475 discloses that “the nicardipine and nicardipine hydrochloride are equally effective in decreasing elevated liver enzymes and bilirubin when administered after the damage to the liver has already occurred and are, therefore, also useful for treatment of liver damage.” (*Id.*).

228. EP ‘475 indicates that “[a]dministration of nicardipine or its salt, preferably nicardipine hydrochloride, can be via any of the accepted modes of administration suitable for treatment of the liver disorder.” (*Id.* at 9).

229. EP ‘475 also indicates that “[t]hese methods include oral routes, parenteral routes such as intravenous, subcutaneous, intradermal, or intramuscular and other systemic routes of administration such as, for example, by suppositories.” (*Id.*).

230. EP ‘475 identifies “oral administration” as the “preferred” route. (*Id.*).

231. EP ‘475 identifies oral dosage forms as “solutions, suspensions, tablets, pills, capsules, powders, sustained release formulations and the like.” (*Id.*).

232. EP ‘475 explains that parenteral administration “would preferably be reserved for crisis situations, wherein the subject is unable to swallow or administer the medication to himself.” (*Id.*).

233. EP '475 defines "[p]arenteral route of administration" as "the administration of drugs to a patient by injection under or through one or more layers of the skin or mucous membrane." (*Id.*).

234. EP '475 indicates that "an effective dosage is in the range of 0.001-5 mg/kg/day, preferably 0.03-1 mg/kg/day." (*Id.*).

235. EP '475 also indicates that "[f]or an average 70 kg human, this would amount to 0.07-350 mg/day, preferably 2-70 mg/day." (*Id.*).

236. EP '475 states that "the manufacture of the pharmaceutical compositions" of nicardipine "may be performed in the usual way." (*Id.* at 10).

237. EP '475 identifies "solid, semi-solid or liquid dosage forms, such as, for example, tablets, pills, capsules, powders, liquids, suspensions, or the like, preferably in unit dosage forms suitable for single administration of precise dosages." (*Id.*).

238. EP '475 indicates that "[t]he pharmaceutical compositions will include a conventional pharmaceutical carrier or excipient" and "may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc." (*Id.*).

239. In particular, EP '475 states that "[l]iquid pharmaceutically administrable compositions can be prepared by dissolving or dispersing, or otherwise preparing a nicardipine or nicardipine salt, and mixing it optionally with a pharmaceutical adjuvant in a carrier, such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form a solution or suspension." (*Id.* at 10-11).

240. EP '475 also states that "[f]or parenteral administration, such as, for example, intravenous injections, the nicardipine or nicardipine salt is dissolved in a vehicle." (*Id.* at 11).

241. EP '475 states that the "[v]ehicle may be, for example, aqueous vehicle, such as sodium chloride injection, Ringer's injection, dextrose injection and others, water miscible vehicle, such as ethyl alcohol, polyethylene glycol of the liquid series or propylene glycol, or nonaqueous vehicles such as corn oil, peanut oil or sesame oil." (*Id.*).

242. EP '475 further states that the "[v]ehicle will be buffered to the proper pH in order to stabilize a solution against chemical degradation and formed in such a way as to control isotonicity of injection." (*Id.*).

243. EP '475 further states that "[o]ther substances may also be added as antimicrobial or antioxidant agents." (*Id.*).

244. EP '475 states generally that "[m]ethods of preparing various pharmaceutical compositions with a certain amount of active ingredient are known, or will be apparent, to those skilled in this art." (*Id.*).

245. EP '475 discloses seven examples of nicardipine hydrochloride formulations. (*Id.* at 17-19).

246. Five of the examples disclosed by EP '475 are solid tablet formulations. (*Id.* at 17-18, Examples 1-5).

247. Example 6 of EP '475 describes an "injectable preparation." (*Id.* at 18).

248. The injectable preparation of Example 6 of EP '475 includes distilled, sterile water as the vehicle, 10 mg/ml of active ingredient, and a phosphate buffer to adjust the pH of the solution to 7. (*Id.*).

249. Example 7 of EP '475 describes an "oral suspension." (*Id.* at 19).

250. The oral suspension of Example 7 of EP '475 includes distilled water as the vehicle, 1 mg/ml of active ingredient, 12.85 grams of a 70% solution of sorbitol, 0.5 grams of

fumaric acid, and other ingredients, such as sodium chloride, methyl paraben, granulated sugar, Veegum K, flavoring and coloring. (*Id.*).

251. EP '475 states that "[f]or parenteral administration, such as, for example, intravenous injections, the nicardipine or nicardipine salt is dissolved in a vehicle."

C. Pharmaceutical Dosage Forms

252. *Pharmaceutical Dosage Forms* (Kenneth E. Avis, Leon Lachman, and Herbert A. Lieberman eds., 1984) ("Pharmaceutical Dosage Forms") explains that "[c]hanges in the pH of a preparation may occur during storage because of degradation reactions within the product, interaction with container components (i.e., glass or rubber), and dissolution of gases and vapors."

253. *Pharmaceutical Dosage Forms* further explains that "buffers are added to many products to resist a change in pH."

254. *Pharmaceutical Dosage Forms* explains that "[a]lthough buffers assure the stability of pH of solution, the buffer system itself can alter other properties such as kinetic and solubility aspects." (*Id.* at 160).

255. *Pharmaceutical Dosage Forms* also explains that "[b]uffers can act as general acid or general base catalysts and cause degradation of the drug substance." (*Id.*).

D. Physical Pharmacy

256. Alfred N. Martin *et al.*, *Physical Pharmacy* (1969) ("Physical Pharmacy") addresses the use of buffers with alkaloidal base solutions.

257. *Physical Pharmacy* teaches that "[p]arenteral solutions for injection into the blood stream are usually not buffered, or they are buffered to a very low capacity so that the buffers of the blood may readily bring them within the physiological pH range."

E. Industrial Pharmacy

258. Industrial Pharmacy explains that “[b]uffer systems must be selected with consideration of their effective range, concentration, and chemical effect on the total product.”

259. Industrial Pharmacy teaches that “[a]cetates, citrates, and phosphates are the principal buffer systems used, but buffer systems making use of other ingredients in the formulation are often used to reduce the total number of ingredients in the product.”

F. Pharmaceutics

260. Pharmaceutics explains “[w]here maximum stability dictates wider [pH] values, it is important for injections that the buffer has a low capacity to prevent unnecessary challenge to the homeostatic [sic] pH 7.4 of blood.”

G. Windheuser

261. John J. Windheuser, *The Effect of Buffers on Parenteral Solutions* (“Windheuser”) is the transcription of a presentation given by an employee of Sandoz Pharmaceuticals at a Meeting of the Parenteral Drug Association.

262. The presentation addresses “the application of buffers and buffer concepts to parenteral solutions.”

263. Specifically, the presentation addressed the “physical chemical concepts associated with buffers,” the “effect of buffers on the stability of the final product,” and the “biological effects of buffers on the body.”

264. Windheuser states:

In most pharmaceutical texts, it is emphasized that buffers are utilized to maintain a stable environmental condition for drugs, the exact condition varying with the nature of the drug itself, but, in most cases, nothing is said about the possibility of buffers endangering the stability of the product. Generally, the impression is given that these buffers are chemically innocuous agents which

can be used without regard to the particular problem. Although I would like to state that I am not trying to dissuade you from using buffers in your own work, I do want to leave you today with the distinct impression that buffers can be detrimental to your product. These buffers may act as general acid or general base catalysts, or they may act as reactive species which, by inter-action with the drug, may result in the formation of a new compound.

H. Cardiovascular Drugs

265. Jun-ichi Imagawa, Keisuke Satoh, and Norio Taira, Coronary Vasodilator and Cardiac Effects of NKY-722, A Novel Hydrophilic 1,4-Dihydropyridine Derivative, in the Blood-Perfused Dog Heart, Cardiovascular Drugs and Therapy (1989) ("Cardiovascular Drugs") is an article that discusses "[t]he coronary vasodilator and cardiac effects of NKY-722," a dihydropyridine calcium antagonist.

I. Secondary Considerations

1. Commercial Success

266. On March 22, 2005, PDL acquired ESP in a transaction valued at approximately \$475 million.

267. Through this transaction, PDL acquired not only the right to market and sell Cardene® I.V., but also, ESP's sales force and marketing personnel.

268. On February 3, 2008, PDL sold the Cardene® I.V. franchise to EKR for \$85 million as an initial purchase price, \$85 million in milestone payments, a 10% royalty on product sales of future line extensions, and a 5% royalty on net sales of another product.

2. Long Felt Need

269. The development of Cardene® I.V. made nicardipine available to patients in which oral treatment is unavailable or undesirable.

270. When the heart has to pump harder to force blood through the narrower arteries, blood pressure rises.

271. The resistance to blood flow as a result of constriction of the arterioles is one of the principal determinants of blood pressure at any given moment.

272. Cardene® I.V. was the first calcium channel blocking agent approved for use as an antihypertensive by the FDA in an injectable formulation.

3. Failure of Others

273. EP '705 and the counterpart '823 patent disclose a nicardipine composition developed by Yamanouchi Pharmaceutical Co. ("Yamanouchi") that includes a polyhydric alcohol ("the Yamanouchi formulation").

4. **CONTESTED FACTS (Proofs shall be limited at trial to the contested facts set forth. Failure to set forth any contested facts shall be deemed a waiver thereof.)**

A. **Plaintiffs:**

I. **BACKGROUND OF TECHNOLOGY**

A. **pH**

1. A low pH indicates that a solution is acidic.
2. A high pH indicates that a solution is basic.

B. **Calcium Channel Blockers**

3. Beta-blockers are effective in lowering heart rate, a component of blood pressure, but may not be ideal, especially in patients with lung disease as they have a tendency to diminish lung function, which can result in respiratory arrest.

4. Further, beta-blockers can mask the effects of hypoglycemia and, therefore, should not be considered a first line agent in patients with diabetics mellitus.

5. In another comparison study between nicardipine hydrochloride and sodium nitroprusside, evidence showed that administration of nicardipine during the first 24 hours reduced the risk of mortality without increasing the hospital cost or length of the stay. (See PDL0132059, Fareed *et al.*, "A Multicenter Comparison of Outcomes With Nicardipine And Nitroprusside For Treatment of Acute Hypertension In Patients With Intracerebral Hemorrhage: Results from the AMUST Study").

6. Calcium ions are one of the most important regulators of muscle contraction, including the heart muscle as well as the smooth muscle surrounding blood vessels.

7. Calcium ions are positively charged and play an important role in the electrical activity of the heart.

8. As compared to the other available drugs, nicardipine hydrochloride has a unique and highly desirable mechanism of action.

9. Specifically, nicardipine hydrochloride selectively targets the arterioles, which are the smallest of the arteries and have the greatest effect on overall blood pressure.

10. Nicardipine hydrochloride offers precise control of blood pressure without objectionable side effects associated with beta-blockers or the titration required with other calcium channel antagonists.

II. PATENT-IN-SUIT

A. Specification

11. The '405 patent teaches that nicardipine hydrochloride is a calcium channel blocking agent that is used for the management of cardiovascular and cerebrovascular disease conditions.

B. Prosecution History

12. The '277 application was a continuation-in-part of United States Application No. 317,171 ("the '171 application"), filed February 28, 1989.

13. During an April 28, 1992 phone interview, Applicants and the Examiner discussed the combination of references over which the claims were finally rejected, along with the Declaration of Alistair B. Selkirk.

C. Level of Ordinary Skill

14. The '405 patent is directed to pharmaceutical formulators in general, not specialists or experts in parenteral formulations.

15. The person of ordinary skill in the art of the '405 patent would have a professional and/or undergraduate degree in pharmacy or a related pharmaceutical field (or an